## REMARKS

A check for $510 for a three-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application during its pendency may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claim 131 is amended herein to correct a typographical error, replacing the recitation "method of claim 124" with the recitation "array of claim 124." No new matter is added.

**PENDING CLAIMS 58-60, 63, 111-113, 127, 133 AND 135**

The Office Action indicates that all claims are rejected. Applicant respectfully submits that pending claims 58-60, 63, 111-113, 127, 133 and 135 are not included in any of the rejections in the Office Action mailed August 19, 2004. Applicant respectfully requests clarification and the opportunity to respond to any rejection of these claims.

**THE REJECTION OF CLAIMS 1-27, 29-33, 35-37, 40-52, 54, 61, 62, 64-70 AND 73-76 UNDER 35 U.S.C. §102(a)**

Claims 1-27, 29-33, 35-37, 40-52, 54, 61, 62, 64-70 and 73-76 are rejected under 35 U.S.C. § 102(a) as anticipated by Köster (WO 94/16101 (July 21, 1994)) because Köster allegedly discloses a method for sequencing a target nucleic acid that includes every element of the claimed subject matter.

This rejection is respectfully traversed. Applicant respectfully submits that the rejection as applied to claims 61 and 62 is moot, as these claims are not pending.

## RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990); *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990); *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl. 1966). *See, also, Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover, it is incumbent on the Examiner

to identify where each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

## THE CLAIMS

Claim 1 is directed to a method for sequencing a target nucleic acid, that includes providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Claims 2-27, 29-33, 35-37, 40-52, 54, 61, 62, 64-70 and 73-76 ultimately depend from claim 1 and are directed to various embodiments thereof.

## ANALYSIS

### DISCLOSURE OF KÖSTER

Köster discloses sequencing DNA using Sanger sequencing and analysis of the nested fragments obtained by base-specific chain termination via their different molecular masses using mass spectrometry. In one embodiment, Köster discloses a solid support-bound capture sequence, where the immobilized nested Sanger fragments can be directly ablated during mass spectrometric analysis (page 15, lines 1-4). In one embodiment, Köster discloses that if all four chain terminating reactions are combined and then analyzed by mass spectrometry, the molecular weight difference between two adjacent peaks can be used to determine the sequence (for example, see page 17, lines 5-20).

### Differences between the claimed subject matter and the disclosure of Köster

Köster discloses directly ablating immobilized nested Sanger fragments from a solid support during mass spectrometric and comparing changes due to specific chain-elongating or chain-terminating bases. Köster does not disclose a method

where hybrids in an array are detected by determining the molecular weight of the hybridized probes. Köster does not disclose that the sequence of the target nucleic acid can be constructed by identifying the hybridized probes. Thus, Köster does not disclose determining molecular weights of nucleic acids in the target array to identify hybridized probes and, based upon the hybridized probes, determining the sequence of the target nucleic acid. Hence, Köster does not disclose every element of claim 1 and its dependent claims. Therefore, Köster does not anticipate claims 1-27, 29-33, 35-37, 40-52, 54, 64-70 or 73-76. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

**THE REJECTION OF CLAIM 28 UNDER 35 U.S.C. §103(a)**

Claim 28 is rejected under 35 U.S.C. §103(a) over Köster (WO 94/16101) in view of Weiss (U.S. 6,025,193) because Köster allegedly teaches all elements of claim 28, except generation of thiol moieties by using Beucage reagent, but Weiss allegedly cures this defect.

This rejection is respectfully traversed.

**RELEVANT LAW**

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd.

APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

**CLAIM 28**

Claim 28 depends from claim 1, and is directed to an embodiment thereof where the array includes nucleic acid probes having as a mass-modifying functionality a thiol moiety that is generated by using Beucage reagent.

**TEACHINGS OF THE CITED ART**

**Köster (WO 94/16101)**

See related section above.

**Weiss (U.S. 6,025,193)**

Weiss teaches methods and compositions for diagnosing and treating pathological conditions related to a dopamine receptor abnormality, which includes administering a plasmid encoding an oligonucleotide anti-sense to one or more RNA molecules encoding one of the several dopamine receptors. The reference teaches that unmodified oligodeoxynucleotides can be converted into phosphorothioate oligodeoxynucleotides using standard phosphoramidite protocols but replacing the standard oxidation by iodine with Beucage reagent for sulfurization. Weiss teaches that using Beucage reagent results in the replacement of every oxygen group of the phosphodiester bond with a sulfur group, and that such substitutions result in an asymmetric distribution of the negative charge to predominate on the sulfur atom, resulting in "improved stability to nucleases, retention of solubility in water and stability to base-catalyzed hydrolysis" (col. 13, lines 2-14), improved biodistribution

and *in vivo* stability (col. 15, lines 41-45), and activation of Rnase H, and thus are potentially useful therapeutic agents (col. 13, lines 45-47).

Weiss does not teach or suggest a method for sequencing a target nucleic acid, that includes providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid.

## ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

### (1) There would have been no motivation to have combined the teachings of Köster with that of Weiss

There would have been no motivation to one of ordinary skill in the art to have combined Köster with Weiss in the manner suggested by the Examiner. Weiss teaches methods and compositions for diagnosing and treating pathological conditions related to a dopamine receptor abnormality. The reference teaches that unmodified oligodeoxynucleotides can be converted into phosphorothioate oligodeoxynucleotides using standard phosphoramidite protocols but replacing the standard oxidation by iodine with Beucage reagent for sulfurization. Weiss teaches that using Beucage reagent results in the replacement of every oxygen group of the phosphodiester bond with a sulfur group, and that such substitutions result in an asymmetric distribution of the negative charge to predominate on the sulfur atom, resulting in "improved stability to nucleases, retention of solubility in water and stability to base-catalyzed hydrolysis", improved biodistribution and *in vivo* stability, and activation of RNAse H. Since Weiss is not concerned with methods for detecting nucleic acid molecules or sequencing nucleic acids, it's teachings are unrelated to the methods of Köster. Accordingly, those of ordinary skill in the art would not have been motivated to have combined the teachings of the references. The advantages of using Beaucage reagent articulated by Weiss are inapplicable to detection or sequencing methods.

**(2) Notwithstanding the lack of motivation, the combination of the teachings of Köster with the teachings of Weiss does not result in the instantly claimed methods.**

As discussed above, Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as an element determining the molecular weight of nucleic acids in the target array to identify hybridized probes, whereby the sequence of the target nucleic acid is determined. Weiss does not cure this defect. Weiss does not teach or suggest sequencing a target nucleic acid. Weiss does not teach or suggest a method that includes any of the steps of providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence in the target nucleic acid, hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, or determining molecular weights for nucleic acids in the target array to identify hybridized probes, whereby the sequence of the target nucleic acid can be determined. Thus, even if Weiss teaches generating thiol moieties using Beucage reagent, Weiss fails to cure the deficiencies in the teachings of Köster.

Neither Köster nor Weiss, individually or in combination, teaches or suggests a method for sequencing a target nucleic acid that includes as an element determining the molecular weight of nucleic acid fragments hybridized in the target array in order to identify hybridized probes and thereby determine the sequence of the target nucleic acid. Thus, combining the teachings of Köster and Weiss does not result in the instantly claimed method of claim 28. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

**THE REJECTION OF CLAIM 34 UNDER 35 U.S.C. §103(a)**

Claim 34 is rejected under 35 U.S.C. §103 as being unpatentable over Köster (WO 94/16101) in view of Cantor (U.S. Patent 5,503,980) because Köster allegedly teaches all elements of claim 34, except ligating the hybridized target nucleic acids to the probes, but Cantor allegedly cures this defect.

This rejection is respectfully traversed.

**RELEVANT LAW**

See related section above.

**CLAIM 34**

Claim 34 depends from claim 1, and is directed to an embodiment thereof further including the step of ligating the hybridized target nucleic acids to the probes.

## TEACHINGS OF THE CITED ART

**Köster (WO 94/16101)**

See related section above.

**Cantor (U.S. Patent 5,503,980)**

Cantor teaches positional sequencing by hybridization. Cantor teaches probes having a double-stranded portion, a single-stranded portion, and a random sequence within the single-stranded portion that is determinable (col. 5, lines 40-45). In one embodiment, Cantor teaches a method for determining a nucleotide sequence by positional hybridization (col. 7, lines 63 through col. 8, line 6). Cantor teaches using hybridization chips with large probe arrays subsequently hybridized with target nucleic acid and determining the target nucleotide sequence by analysis of the hybridization pattern on the chip, which provides a fingerprint identification of the target nucleotide sequence (col. 7, lines 6-10).

Cantor does not teach or suggest a method for sequencing a target nucleic acid that includes providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid.

## ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of prima facie obviousness for the following reasons.

**The combination of the teachings of Köster with the teachings of Cantor does not result in the instantly claimed methods.**

As discussed above, Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as an element determining molecular weights of nucleic acids in the target array to identify hybridized probes, and based upon the hybridized probes, determining the sequence of the target nucleic acid. Cantor does not cure this defect. Cantor teaches arrays of probes that are partially double-stranded and partially single-stranded. There is no teaching or suggestion in Cantor to determine the molecular weights of nucleic acid fragments hybridized in a

target array in order to identify hybridized probes and thereby determine the sequence of the target nucleic acid. The only teachings directed to molecular weight in Cantor are the teaching in Example 2 directed to fractionation of a sample, and reference to the Maxim and Gilbert sequencing technique, where terminally labeled DNA molecules are chemically cleaved at single base repetitions and then the molecular weight of each partially cleaved fragment is determined using electrophoresis to produce a pattern of fragments on a gel, whereby the DNA sequence can be read (see col. 1, lines 24-35). Hence, Cantor does not teach or suggest determining molecular weights of nucleic acids in the target array to identify hybridized probes, whereby the sequence of the target nucleic acid is determined. Hence, Cantor does not teach or suggest the subject matter missing from the teachings of Köster.

Thus, even if Cantor teaches ligating the hybridized target nucleic acids to the probes, combining the teachings of Köster and Cantor does not result in a method for sequencing a target nucleic acid that includes as a step determining molecular weights of nucleic acids in the target array to identify hybridized probes, and based upon the hybridized probes, determining the sequence of the target nucleic acid. Hence, the combination of Köster and Cantor does not teach or suggest every element of claim 34. Therefore, the Examiner has failed to set forth a prima facie case of obviousness. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

**THE REJECTION OF CLAIMS 71 AND 72 UNDER 35 U.S.C. §103(a)**

Claims 71 and 72 are rejected under 35 U.S.C. §103 as being unpatentable over Köster (WO 94/16101) in view of Sanghvi *et al.* (U.S. Patent No. 6,214,551) because Köster allegedly teaches all elements of the claims except that the selectively releasable bond is 4,4'-dimethoxytrityl or a derivative thereof, and Sanghvi *et al.* allegedly cures this defect. The Examiner contends that Sanghvi *et al.* teaches the selectively releasable bond 4,4'-dimethoxytrityl or a derivative thereof, and argues that although the reference does not teach the derivative 3 or 4 [bis-(4-methoxy-phenyl)]-methyl-benzoic acid in particular, Sanghvi *et al.* teaches equivalent compounds and derivatives used for the same purpose.

This rejection is respectfully traversed.

## THE CLAIMS

Claims 71 and 72 ultimately depend from claim 1 and are directed to various embodiments thereof. Claim 71 is directed to the embodiment where each probe is attached to the solid support by a selectively releasable bond that includes 4, 4'-dimethoxytrityl or a derivative thereof. Claim 72 is directed to the embodiment where the derivative of 4, 4'-dimethoxytrityl is selected from the group consisting of 3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-methyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-hydroxymethyl-benzoic acid, N-succinimidyl-3 or 4 [bis-(4-methoxyphenyl)]-chloromethyl-benzoic acid and salts thereof.

## RELEVANT LAW

See related section above.

## TEACHINGS OF THE CITED ART

**Köster (WO 94/16101)**

See related section above.

**Cantor (U.S. Patent 5,503,980)**

See related section above.

**Sanghvi *et al.* (U.S. Patent 6,214,551)**

Sanghvi *et al.* teaches compounds that mimic and/or modulate the activity of wild-type nucleic acids. The compounds taught by Sanghvi *et al.* contain a selected nucleotide sequence where the nucleotides are covalently bound through linking groups that contain adjacent nitrogen atoms. Sanghvi *et al.* teaches the use of dimethoxytrityl groups as a blocking group during nucleoside polymerization. Sanghvi *et al.* teaches that an oligonucleotide is tethered to a solid support via its 3' hydroxyl group (col. 57, line 63 through col. 58, line 14).

Sanghvi *et al.* does not teach or suggest the use of dimethoxytrityl or a derivative thereof as a selectively releasable bond by which to attach a probe to a solid support. Sanghvi *et al.* does not teach or suggest using mass spectrometry, or using mass spectrometry for sequencing nucleic acids, or hybridizing a set of nucleic acid fragments containing a sequence that corresponds to a sequence of the target nucleic acid to an array of nucleic acid probes to form a target array of nucleic acids.

Sanghvi *et al.* does not teach or suggest identifying hybridized probes by molecular weight, whereby the sequence of the target nucleic acid is determined.

## ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

**The combination of teachings of Köster with the teachings of Sanghvi *et al.* does not result in the instantly claimed methods.**

As discussed above, Köster does not teach or suggest methods for sequencing a target nucleic acid that include as an element determining the molecular weight of nucleic acids in the target array to identify hybridized probes, whereby the sequence of the target nucleic acid is determined. Sanghvi *et al.* does not cure this defect. Sanghvi *et al.* does not teach or suggest using mass spectrometry, or using mass spectrometry for sequencing nucleic acids, or hybridizing a set of nucleic acid fragments containing a sequence that corresponds to a sequence of the target nucleic acid to an array of nucleic acid probes to form a target array of nucleic acids. Sanghvi *et al.* does not teach or suggest determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Hence, Sanghvi *et al.* does not teach or suggest the subject matter missing from the teachings of Köster.

Accordingly, even if, arguendo, Sanghvi *et al.* teaches selectively releasable bonds containing 4,4'-dimethoxytrityl or a derivative thereof, which applicant contends is not taught by Sanghvi *et al.*, the combination of Köster and Sanghvi *et al.* does not teach or suggest all the elements of the claimed methods.

Neither Köster nor Sanghvi *et al.*, alone or in combination, teaches or suggests a method for sequencing a target nucleic acid that includes as an element determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Thus, combining the teachings of Köster and Sanghvi *et al.* does not result in the instantly claimed methods of claims 71 and 72. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

**THE REJECTION OF CLAIMS 38, 39, 53, 55, 86, 88-110, 114-124, 128-132, 134 AND 136-144 UNDER 35 U.S.C. §103(a)**

Claims 38, 39, 53, 55, 86, 88-110, 114-124, 128-132, 134 and 136-144 are rejected under 35 U.S.C. § 103(a) over Köster (WO 94/16101) in view of Cantor (U.S. 5,503,980), because Köster allegedly teaches all elements of the claimed subject matter except probes that include a double-stranded portion and a single-stranded portion, probes having 10-1,000 nucleotides, probes having a variable region of about 4-20 nucleotides in length, fragments of nucleic acids including greater than about $10^4$ different members or arrays of probes having sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination, but Cantor allegedly cures these defects.

This rejection is respectfully traversed.

**RELEVANT LAW**

See related section above.

**THE CLAIMS**

Claim 1 is directed to a method for sequencing a target nucleic acid, that includes providing a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid; hybridizing the set to an array of nucleic acid probes to form a target array of nucleic acids, where each probe includes a single-stranded portion including a variable region such that each member of the set hybridizes to a member of the array of probes; determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Claims 38, 39, 53, 55, 89-103, 114-124, 128, ultimately depend from claim 1 and are directed to various embodiments thereof.

Claim 124 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion and a constant double-stranded portion; each single-stranded portion includes a variable sequence; the array of probes has sufficient sequence diversity in the variable regions to hybridize to all of a target nucleic acid molecule with complete or nearly complete discrimination; the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry; and the array includes a nucleic acid probe

having at least one mass-modifying functionality that increases the discrimination between at least two nucleic acid molecules when detected by mass spectrometry. Claims 129-144 ultimately depend from claim 124 and are directed to various embodiments thereof.

Claim 86 depends from claim 127, which is directed to a system including a mass spectrometer, a computer and the array of claim 124.

## TEACHINGS OF THE CITED ART

**Köster (WO 94/16101)**

See related section above.

**Cantor (U.S. Patent 5,503,980)**

See related section above.

## ANALYSIS

**1. Claims 38, 39, 53, 55, 88-110, 114-123 and 128 - Methods**

Claims 38, 39, 53, 55, 88-110, 114-123 and 128 ultimately depend from claim 1. As discussed above in the traverse of the rejection of claim 34 under 35 U.S.C. §103 as being unpatentable over Köster (WO 94/16101) in view of Cantor (U.S. Patent 5,503,980), Köster does not teach or suggest a method for sequencing a target nucleic acid that includes as an element determining molecular weights of nucleic acids in the target array to identify hybridized probes; and based upon the hybridized probes, determining the sequence of the target nucleic acid. Cantor does not cure this defect. Cantor does not teach or suggest determining the molecular weights for nucleic acids of the target array to identify hybridized probes, whereby the sequence of the target nucleic acid is determined. Thus, combining the teachings of Köster and Cantor does not teach or suggest the subject matter claimed in claim 1. Claims 38, 39, 53, 55, 88-110, 114-123 and 128 ultimately depend from claim 1. Hence, the combination of the teachings of Köster and Cantor does not teach or suggest the methods claimed in claims 38, 39, 53, 55, 88-110, 114-123 and 128. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

**2. Claims 129-132, 134 and 136-144 - Arrays**

Claims 129-132, 134 and 136-144 depend from claim 124, which is directed to an array of nucleic acid probes. Köster does not teach or suggest an array of nucleic

acid probes where the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry.

Cantor does not cure this defect. Cantor does not teach or suggest an array of nucleic acid probes where the array is attached to a solid support that includes a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry. The only "matrix" taught be Cantor is an embodiment of the solid support itself. For example, see col. 6, line 64 through col. 7, line 1, which recites:

> Preferred examples of a solid support include a plastic, a ceramic, a metal, a resin, a gel, and a membrane. A more preferred embodiment comprises a two-dimensional or three-dimensional matrix, such as a gel, with multiple probe binding sites, such as a hybridization chip...

Hence, combining the teachings of Köster and Cantor does not teach or suggest an array of nucleic acid probes as instantly claimed, that includes as an element that the array is attached to a solid support including a matrix material that facilitates the volatilization of nucleic acids for mass spectrometry. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

**3. Claims 86 and 127 - Systems**

Claim 86 depends from claim 127, which is directed to a system including a mass spectrometer, a computer and the array of claim 124. As discussed above, the combination of the teachings of Köster and Cantor does not result in the instantly claimed array of 124. Hence, combining the teachings of Köster and Cantor does not result in the systems as claimed in claims 86 and 127.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,

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